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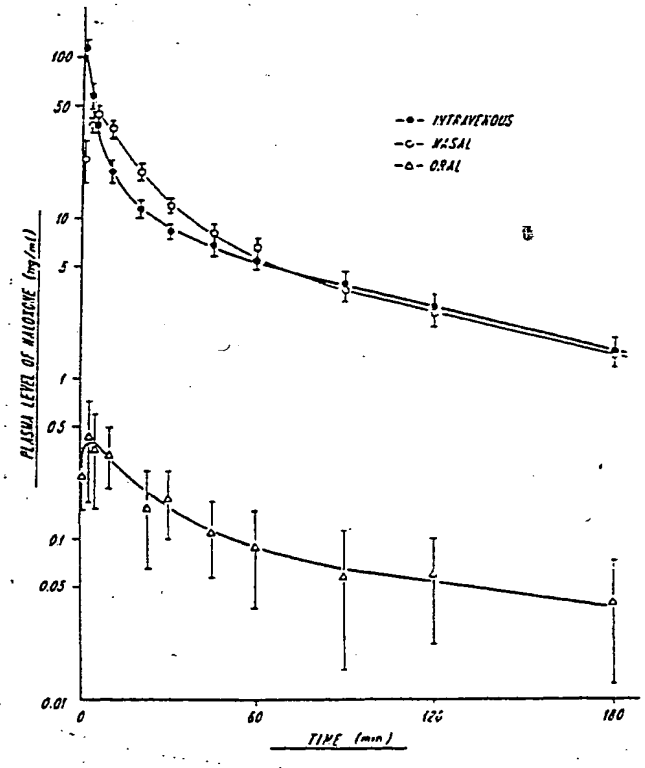
(54) Title: NOVEL METHOD OF ADMINISTERING NARCOTIC ANTAGONISTS AND ANALGESICS AND NOVEL DOSAGE FORMS CONTAINING SAME

(57) Abstract

A novel method of administering narcotic antagonists, narcotic analgesics and related compounds, and dosage forms containing those compounds which are adapted for nasal administration. The nasal dosage forms disclosed include solutions, suspensions, gels and ointments. The compound administered can be morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, or Δ^9-tetrahydrocannabinol or a pharmacologically active analogue thereof bearing at least one phenolic hydroxyl substituent. Especially preferred compounds which can be advantageously administered in accordance with the invention include naloxone, naltrexone, nalbuphine, levorphanol, buprenorphine, butorphanol, Δ^9-tetrahydroxannabinol (THC), cannabidiol (CBD) and levonantradol. The novel dosage forms of the invention include nasal ointments, nasal gels and isotonic nasal compositions containing the selected compound in the form of the free base, or in the case of morphine and its analogues, optionally in the form of a nontoxic pharmaceutically acceptable acid addition salt; and sustained release nasal dosage forms containing a long chain carboxylic acid salt of morphine or an analogue thereof.



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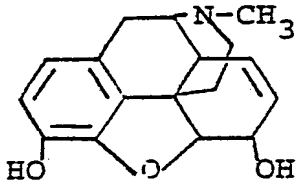
NOVEL METHOD OF ADMINISTERING NARCOTIC ANTAGONISTS AND ANALGESICS AND NOVEL DOSAGE FORMS CONTAINING SAME

FIELD OF THE INVENTION:

The present invention relates to a novel method of administering narcotic antagonists, narcotic analgesics and related compounds, and to novel dosage forms containing such compounds adapted for nasal administration.

BACKGROUND ART:

Morphine, which has the structural formula



is a potent narcotic analgesic which is principally used to relieve pain; it is also used in the dyspnea of heart failure, in pulmonary edema and cough, as a sedative and in the control of diarrhea (chiefly in the form of paragoric). Morphine causes both depression and stimulation in the central nervous system and the gut, its most significant actions being analgesia, hypnosis, respiratory depression, smooth muscle spasm, nausea, vomiting and circulatory and other effects (especially miosis). The drug is well-absorbed by injection, but absorption via the oral route is inefficient and variable, probably because of metabolism in the liver, chiefly by conjugation with glucuronic acid. Abuse leads to habituation or addiction.

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The morphine molecule has been subjected to a variety of structural modifications in efforts to enhance selected properties and/or to deemphasize others, as well as to produce drugs which actually antagonize the effects of morphine and other opioid analgesics. Such efforts have led to the development of a variety of classes of chemical compounds, such as the class of morphine analogues whose structures are very closely allied to that of morphine, retaining both the phenolic OH and the N-methyl substituent of morphine, such as apomorphine, levorphanol and oxymorphone, and which as a group have strong analgesic, respiratory depressant and smooth muscle stimulant activity but which also are highly addicting. Retention of the phenolic hydroxyl while replacing the methyl on the nitrogen atom with a larger alkyl or similar side-chain has afforded both morphine analogues which are relatively pure opioid antagonists (e.g. naloxone and naltrexone) and are used in the treatment of narcotic-induced respiratory depression (overdose), in the diagnosis of narcotic addiction and in the prophylaxis of narcotic abuse; and morphine analogues which are agonist-antagonists (e.g. buprenorphine, pentazocine, nalorphine and cyclazocine), which display varying degrees of morphine-like activity as well as of morphine-antagonist behavior, and which can therefore be used as analgesics as well as for the purposes for which the relatively pure antagonists are used.

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Buprenorphine appears to be a particularly valuable analogue because of its low physical dependence potential, as well as its potent narcotic antagonist and analgesic activity. See Cowan et al, Br. J. Pharmac. (1977), 60, 537-545; Jasinski et al, Arch Gen. Psychiatry, Vol. 35, April 1978, 501-516; Mello et al, Science, Vol. 207, 8 February 1980, 657-659.

Virtually all of the members of the groups of morphine analogues discussed supra are well-absorbed by injection, but are rarely used orally because of inefficient and variable absorption by that route. The low effectiveness of naloxone when taken orally has been attributed to the rapid and almost total formation of a less active metabolite in the first hepatic transit. See Fishman et al, J. Pharmacol. Exp. Ther. 187, 575-580 (1973). Also Berkowitz et al, J. Pharmacol. Exp. Ther. 195, 499-504, and the references cited therein.

Yet other structural modifications of the morphine molecule have resulted in codeine and its analogues; methadone and related compounds; and meperidine and related compounds such as profadol. Also see, generally, Pharmacological Basis of Therapeutics, ed. Goodman and Gilman, sixth edition, Chapter 22, "Opioid Analgesics and Antagonists", by Jaffe and Martin, pp. 494-534 (MACMILLAN PUBLISHING CO., INC., New York, 1980); Cutting's Handbook of Pharmacology, sixth edition, ed. T. Z. Czáky, M.D., Appleton-Century-Crofts/New York, Chapter 50, pp. 551-571.

Recent studies of THC, or Δ^9-tetrahydrocannabinol, which is the active ingredient in marijuana, or its derivatives (e.g. CBD or cannabidiol, and levonantradol) suggest that these compounds are

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potentially useful in a wide variety of therapeutic areas, such as in the prevention of narcotic withdrawal symptoms and as antiemetics, particularly in the treatment of cancer patients undergoing chemotherapy. Unfortunately, oral administration has been found to be much less effective than intramuscular injection. See, Medical News, Monday, January 19, 1981, page 3, for a more detailed discussion of the various therapeutic uses of THC and its derivatives.

SUMMARY OF THE INVENTION:

In view of the foregoing, it is apparent that a serious need exists for the improved delivery of narcotic antagonists, narcotic analgesics and related compounds which are not well-absorbed orally. Thus, it is an object of the present invention to provide novel dosage forms and a novel method of administering morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, or Δ^9-tetrahydrocannabinol or a pharmacologically active analogue thereof bearing at least one phenolic hydroxyl substituent, which will provide greatly enhanced bioavailability as compared to oral administration, while at the same time providing relative ease of administration when compared to intramuscular, subcutaneous or intravenous injection. This object is achieved by nasal administration of morphine, Δ^9-tetrahydrocannabinol, or one of their aforesaid phenolic, pharmacologically active analogues, advantageously

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formulated into a solution, suspension, ointment or gel adapted for nasal administration.

In one aspect, the present invention thus provides a pharmaceutically acceptable nasal dosage form for nasally delivering systemic therapeutic levels of drug to a warm-blooded animal which comprises (i) a systemically therapeutically effective amount of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, or Δ^9-tetrahydrocannabinol or a pharmacologically active analogue thereof bearing at least one phenolic hydroxyl substituent, and (ii) a nontoxic pharmaceutically acceptable nasal carrier therefor, said nasal dosage form comprising a nasal ointment or a nasal gel.

In another aspect, the present invention provides a pharmaceutically acceptable sustained release nasal dosage form for nasally delivering systemic therapeutic levels of drug to a warm-blooded animal which comprises (i) a systemically therapeutically effective amount of a long chain carboxylic acid salt of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, and (ii) a nontoxic pharmaceutically acceptable nasal carrier therefor.

In yet another aspect, the present invention provides a pharmaceutically acceptable, isotonic nasal dosage form for nasally delivering systemic therapeutic levels of drug to a warm-blooded animal, which

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comprises (i) a systemically therapeutically effective amount of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, or Δ^9-tetrahydrocannabinol or a pharmacologically active analogue thereof bearing at least one phenolic hydroxyl substituent, and (ii) a nontoxic pharmaceutically acceptable nasal carrier therefor, said nasal dosage form having been adjusted to isotonicity.

BRIEF DESCRIPTION OF THE DRAWING:

The figure of drawing is a semi-logarithmic plot of mean plasma levels of naloxone after intravenous, nasal and oral administration of a dose of 30 µg of naloxone per rat.

DETAILED DESCRIPTION OF THE INVENTION:

The narcotic analgesics, narcotic antagonists and narcotic agonist-antagonists intended for use in the compositions and method of the present invention include morphine and pharmacologically active analogues thereof having at least one aromatic ring, said ring bearing at least one free OH group. Particularly significant morphine analogues contemplated by the present invention include morphine-like analgesics such as apomorphine, hydromorphone, levorphanol, metopon and oxymorphone; and narcotic antagonists and agonist-antagonists such as buprenorphine, diprenorphine, butorphanol, cyclazocine, pentazocine, phenazocine, levallorphan, nalorphine, naloxone, alazocine, nalbufine, oxilorphan, nalmexone and naltrexone. Other analogues contemplated

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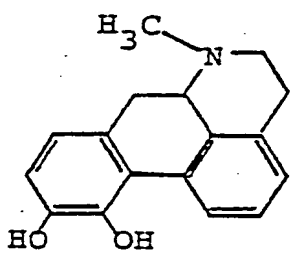
by the invention include ketobemidone, apocodeine, profadol, cyclorphan, cyprenorphine, desomorphine, dihydromorphine, 3-hydroxy-N-methylmorphinan, levophenacylmorphan, metazocine, norlevorphanol, oxymorphone, phenomorphan, pholcodine, and hydroxypethidine. Especially preferred morphine analogues are those having antagonist or agonist-antagonist properties, especially naloxone, nalbufine, naltrexone, buprenorphine and butorphanol. Any pharmaceutically acceptable form of morphine or of its phenolic analogues can be used, i.e. the free base or a pharmaceutically acceptable acid addition salt thereof (e.g. naloxone hydrochloride, nalbufine hydrochloride, nalorphine hydrochloride, nalorphine hydrobromide, levallorphan tartrate, morphine sulfate, levorphanol tartrate, buprenorphine hydrochloride, butorphanol tartrate, pentazocine lactate, pentazocine hydrochloride, phenazocine hydrobromide, morphine hydrochloride, profadol hydrochloride, etc.); generally, the selected compound is employed in the instant compositions and method in the pharmaceutically acceptable form which has previously been found most advantageous for use by injection or orally. The structural formulae for representative free bases encompassed by the present invention are set forth below:

apomorphine



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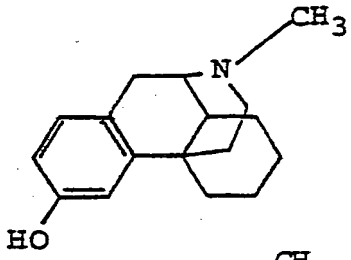
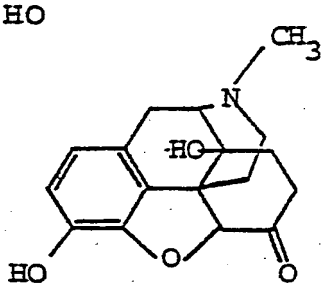
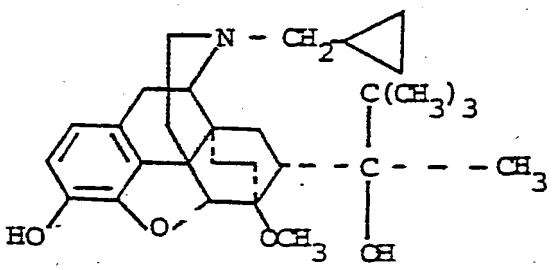
levorphanol



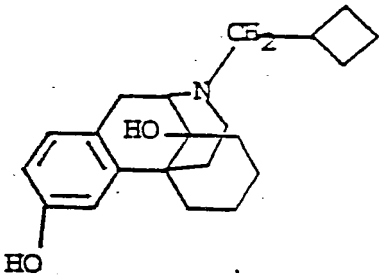
oxymorphone



buprenorphine



butorphanol



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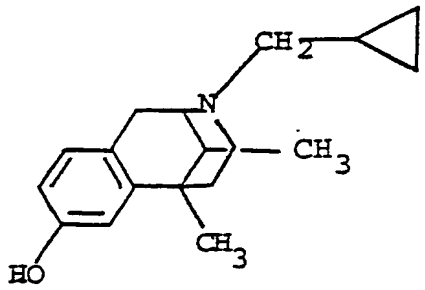
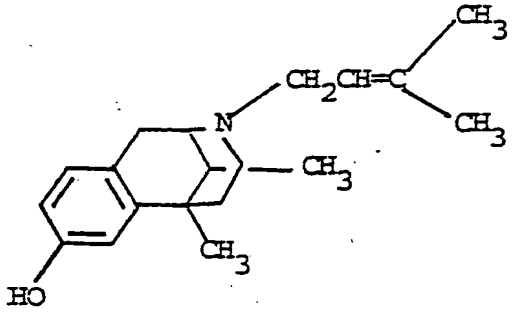
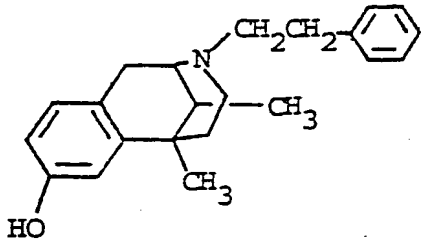
cyclazocine



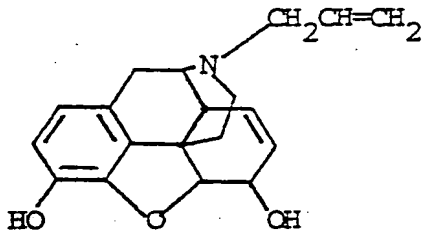
pentazocine



phenazocine



nalorphine



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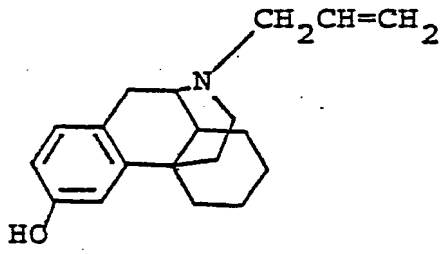
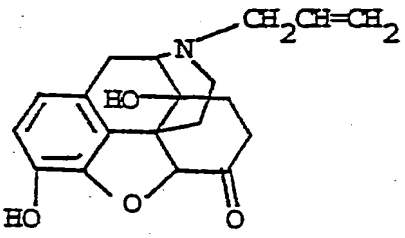
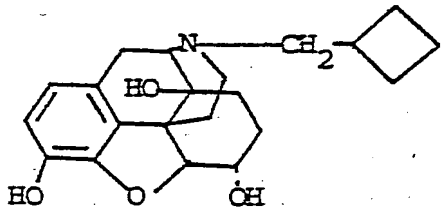
levallorphan



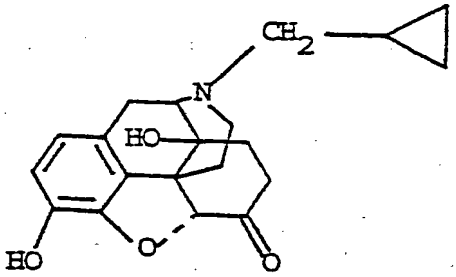
naloxone



nalbufine



naltrexone



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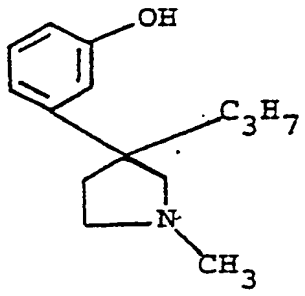
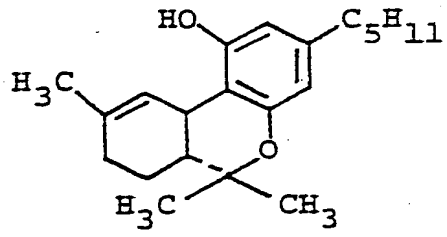
profadol



These morphine analogues and their salts can be prepared by well-known methods. Morphine itself can of course be isolated from natural sources and then converted, if desired, into a pharmaceutically acceptable acid addition salt.

The cannabinoids intended for use in the method and compositions of the present invention include Δ^9-tetrahydrocannabinol (THC) and pharmacologically active derivatives thereof having at least one free OH group on an aromatic ring thereof.

Δ^9-Tetrahydrocannabinol has the structural formula



Preferred derivatives thereof for use in the present invention include cannabidiol (CBD) and levonantradol.

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These compounds can be prepared by known methods or, in the case of THC and CBD, isolated from natural sources.

In accord with the present invention, morphine, THC and their pharmacologically active phenolic analogues can be administered nasally with results considerably superior to those obtained with oral administration in terms of enhanced drug bioavailability and minimization of blood level variations, thus enabling use of these drugs at the dosage levels previously possibly only by injection without the disadvantages inherent in subcutaneous, intramuscular or intravenous administration. It would appear that these drugs are rapidly absorbed from the nasal mucosa into systemic blood without extensive metabolism in the gastrointestinal tract and/or extensive first-pass metabolism.

The following study was undertaken to examine the bioavailability of a representative drug employed in the method and compositions of the invention, namely naloxone, administered nasally, in comparison with the bioavailability of that drug when administered orally and intraveneously.

Sprague-Dawley male rats, each weighing about 270 grams, were used in the study. Three groups of three rats each were employed, one group for each route of administration. The rats were anesthetized

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with pentobarbital (50 mg/kg) prior to administration of the drug. Naloxone was administered at a dose of 30 µg/rat (~40µCi/rat) as ^{3}H-naloxone in 0.1 ml of isotonic saline. For intravenous administration, the drug was injected through the femoral vein. For oral (intraduodenal) administration, the abdomen of each rat was opened through a midline incision and the drug was injected directly through the duodenum. For nasal administration, an incision was made in the neck of each rat and the trachea was cannulated with a polyethylene tube. Another tube was inserted from the esophagus to the posterior part of the nasal cavity, and the nasoplantine was closed with an adhesive agent to prevent drainage of the drug from the nasal cavity to the mouth. The drug was then administered to the nasal cavity through the tube by means of a syringe. Blood was sampled periodically from the femoral aorta. Unchanged radiolabelled naloxone was analyzed according to the procedure described by Fishman et al, J. Pharmacol. Exp. Ther. 187, 575-580 (1973). The method involved centrifugation of the blood and spiking the plasma samples with cold naloxone. The drug was then extracted from the plasma with ethyl acetate. The ethyl acetate extract was then spotted onto thin layer chromatographic plates and the plates were developed in a 100:60:2 chloroform-methanol-acetic acid system (parts by volume). The zone corresponding to free naloxone visualized by ultraviolet absorption was removed and the radioactivity counted.

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TABLE I below shows the individual plasma level data of naloxone from intravenous (PART A), nasal (PART B) and oral (PART C) routes, while the figure of drawing shows the mean plasma levels of naloxone for the different routes of administration. TABLE II below shows the area under the curve values (AUC $\overset{\infty}{0}$) for the individual rats for each of the three routes of administration, the bioavailability calculated for the nasal and oral routes, and the half-lives of elimination of the drug after intravenous and nasal administration.

TABLE I (PART A)

PLASMA LEVELS OF NALOXONE AFTER INTRAVENOUS ADMINISTRATION OF 30 µg/RAT (40 µCi/RAT) OF ^{3}H-NALOXONE IN INDIVIDUAL RATS

Time (Min.)	Plasma Level (ng/ml) I	II	III	Mean	SE
1	101.65	91.45	138.57	110.56	14.31
3	52.28	44.00	77.77	58.02	10.16
5	31.38	33.03	47.93	37.45	5.26
10	15.60	16.92	26.34	19.62	3.38
20	10.27	11.44	13.01	11.57	0.79
30	7.28	9.16	8.59	8.34	0.56
45	5.47	7.98	6.77	6.74	0.72
60	4.87	5.82	5.54	5.41	0.28
90	3.01	4.63	4.23	3.96	0.49
120	2.15	3.87	2.57	2.86	0.52
180	1.25	1.77	1.40	1.47	0.15

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TABLE I (PART B)

PLASMA LEVELS OF NALOXONE AFTER NASAL ADMINISTRATION OF 30 µg/RAT (40 µCi/RAT) of ^{3}H-NALOXONE IN INDIVIDUAL RATS

Time (Min.)	Plasma Level (ng/ml) I	II	III	Mean	SE
1	36.20	12.71	20.97	23.29	6.88
3	41.21	30.85	42.80	38.29	3.75
5	54.45	33.41	44.15	44.00	6.07
10	45.30	31.53	31.02	35.95	4.68
20	22.73	17.68	17.99	19.47	1.63
30	13.46	11.83	10.79	12.03	0.78
45	9.36	7.95	6.56	7.96	0.81
60	8.26	5.98	4.98	6.41	0.97
90	4.79	3.16	2.80	3.58	0.61
120	3.65	2.29	1.84	2.59	0.54
180	1.95	1.22	1.10	1.42	0.27

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TABLE I (PART C)

PLASMA LEVELS OF NALOXONE AFTER ORAL ADMINISTRATION OF 30 µg/RAT (40 µCi/RAT) OF ^{3}H-NALOXONE IN INDIVIDUAL RATS

Time (Min.)	Plasma Level (ng/ml) I	II	III	Mean	SE
1	0.22	0.10	1.43	0.25	0.10
3	0.44	0.15	0.74	0.44	0.30
5	0.18	0.30	0.64	0.37	0.24
10	0.22	0.15	0.64	0.34	0.15
20	0.19	0.03	0.25	0.16	0.11
30	0.28	0.10	0.17	0.18	0.09
45	0.13	0.05	0.16	0.11	0.06
60	0.10	0.02	0.14	0.09	0.06
90	0.04	0.03	0.12	0.06	0.05
120	0.03	0.06	0.10	0.06	0.04
180	0.03	0.02	0.07	0.04	0.03

TABLE II

AREA UNDER THE BLOOD LEVEL CURVE VALUES (AUC $\overset{\infty}{0}$) FOR INDIVIDUAL RATS FROM THE THREE ROUTES OF ADMINISTRATION OF NALOXONE AND HALF-LIVES OF ELIMINATION OF NALOXONE FOLLOWING INTRAVENOUS AND NASAL ADMINISTRATION

	I	II	III	Mean	SE	$t_{1/2}^{\beta}$
IV	1269.7	1540.5	1685.8	1498.7	121.9	59.2 min.
Nasal	1904.2	1336.2	1312.0	1517.5	193.5	52.1 min.
Oral	19.1	11.3	35.5	22.0	7.1	———

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TABLE II, continued

BIOAVAILABILITY CALCULATIONS:

$$\frac{\text{AUC nasal}}{\text{AUC iv}} \times 100 = 1.013 \times 100 = 101.3\%$$

$$\frac{\text{AUC oral}}{\text{AUC iv}} \times 100 = 0.015 \times 100 = 1.5\%$$

It can be seen from TABLE II that the areas under the curve following intravenous and nasal administration were not significantly different, i.e. absorption of naloxone via the nasal route of administration was as effective as via the intravenous route. On the other hand, oral administration of 30 µg of naloxone resulted in bioavailability equal to only 1.5% that of the same dose given intravenously. Also from TABLE II, it can be seen that the nasal bioavailability of naloxone was nearly 70 times greater than the oral bioavailability.

It also can be seen from TABLE I and the figure of drawing that naloxone was very rapidly absorbed from the nasal mucosa; thus, at the 30 µg dosage level, the peak plasma level was attained in about 5 minutes after instillation of the nose drops. Further, the half-life of elimination of the drug after nasal administration was found to be comparable to its half-life following intravenous nasal administration.

The study described above indicates that naloxone is rapidly absorbed from the nasal mucosa into the systemic circulation without extensive intestinal

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or first pass metabolism. It is further apparent from this study that the bioavailability of naloxone when administered nasally is equivalent to the bioavailability of the drug when administered intravenously and vastly superior to its bioavailability by the oral route. As the phenolic hydroxyl group in naloxone is believed to be responsible for the extensive metabolism seen when the drug is administered orally and, consequently, for the drug's poor oral bioavailability, it follows that similar improvement in bioavailability for nasal versus oral administration will be observed in the case of the other phenolic drugs intended for use in the method and compositions of the present invention.

Any of the selected drugs intended for use in the present invention, i.e. morphine, THC or one of their pharmacologically active phenolic analogues, can be administered nasally to warm-blooded animals, conveniently by formulation into a nasal dosage form comprising the desired drug, in a therapeutically effective amount (i.e., depending on the selected drug, an analgesically effective amount, an antiemetic effective amount, an amount effective to antagonize the effects of a narcotic agent, etc.), together with a nontoxic pharmaceutically acceptable nasal carrier therefor. This type of composition can be used in the treatment of any of the variety of conditions which are responsive to treatment with the selected drug itself by other routes of administration.

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As indicated earlier, in the compositions of the invention, the drug can be employed in the form of the free base or, in the case of morphine and its analogues, in the form of a pharmaceutically acceptable salt thereof. Suitable nontoxic pharmaceutically acceptable nasal carriers will be apparent to those skilled in the art of nasal pharmaceutical formulations. For those not skilled in the art, reference is made to the text entitled "REMINGTON'S PHARMACEUTICAL SCIENCES", 14th edition, 1970. Obviously, the choice of suitable carriers will depend on the exact nature of the particular nasal dosage form desired, e.g., whether the drug is to be formulated into a nasal solution (for use as drops or as a spray), a nasal suspension, a nasal ointment or a nasal gel. Preferred nasal dosage forms are solutions, suspensions and gels, which contain a major amount of water (preferably purified water) in addition to the active ingredient . Minor amounts of other ingredients such as pH adjusters (e.g., a base such as NaOH), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present. Most preferably, the nasal composition is isotonic, i.e. it has the same osmotic pressure as blood serum. If desired, sustained release nasal compositions, e.g. sustained release gels, can be readily prepared, preferably by employing the

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desired drug in one of its relatively insoluble forms, such as the free base or an insoluble salt. In the case of morphine and its analogues, when the free base is not sufficiently insoluble for sustained release compositions, or when a more highly insoluble form is desired, a long chain carboxylic acid salt of the desired drug can be conveniently employed. The carboxylic acid portion of the salt preferably contains 10 to 20 carbon atoms. Such salts (e.g. stearates, palmitates etc.) can be readily synthesized, for example, by dissolving the hydrochloride salt of the drug in the water, then adding the alkali metal salt of the desired long chain carboxylic acid (e.g. sodium stearate). The corresponding long chain carboxylic acid salt of the drug which precipitates out of the solution is removed by filtration. Alternatively, equimolar amounts of the free base of the drug and the long chain carboxylic acid are combined in methanol. That mixture is then added to a small volume of water, causing the desired salt (e.g. stearate) of the drug to precipitate out.

Examples of the preparation of typical nasal compositions containing selected drugs are set forth below. However, it is to be understood that these examples are given by way of illustration only and are not to be construed as limiting the invention either in spirit or in scope as many modifications both in materials and in methods will be apparent to those skilled in the art.

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EXAMPLE 1

1 Gram of naloxone hydrochloride is dissolved in 80 ml of distilled water and the pH of the resultant solution is adjusted to 7.4 with dilute sodium hydroxide solution. A quantity of water sufficient to bring the total volume to 100 ml is then added and sufficient sodium chloride (or other appropriate salt) is added to adjust the solution to isotonicity. The solution is then sterilized by being passed through a 0.2 micron Millipore filter. The final composition contains 1 mg of naloxone hydrochloride per 0.1 ml of solution.

The above procedure is repeated using 1 gram of levallorphan tartrate in place of the naloxone hydrochloride. The resultant composition contains 1 mg of levallorphan tartrate per 0.1 ml of solution.

Repetition of the procedure of the first paragraph of this example using 5 grams of apomorphine hydrochloride, 3 grams of hydromorphone hydrochloride, 4 grams of metopon hydrochloride, 1.5 grams of oxymorphone hydrochloride, 0.6 grams of buprenorphine hydrochloride, 2 grams of butorphanol tartrate, 3 grams of pentazocine hydrochloride, 3 grams of phenazocine hydrobromide or 5 grams of nalorphine hydrochloride in place of the naloxone hydrochloride affords a nasal composition containing, respectively, 5 mg of apomorphine hydrochloride, 3 mg of hydromorphone hydrochloride, 4 mg of metopon hydrochloride, 1.5 mg of oxymorphone hydrochloride, 0.6 mg of buprenorphine hydrochloride, 2 mg of butorphanol tartrate, 3 mg of

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pentazocine hydrochloride, 3 mg of phenazocine hydrobromide, or 5 mg of nalorphine hydrochloride, per 0.1 ml of solution.

EXAMPLE 2

15 Grams of nalbufine hydrochloride are combined with 80 ml of distilled water and the pH is adjusted to 4.5 with dilute sodium hydroxide solution. A quantity of water sufficient to bring the total volume to 100 ml is then added and sufficient sodium chloride is added to adjust the solution to isotonicity. The solution is then sterilized by being passed through a 0.2 micron Millipore filter. The resultant composition contains 15 mg of nalbufine hydrochloride per 0.1 ml.

The procedure described above is substantially repeated, except that 15 grams of morphine sulfate are used in place of the nalbufine hydrochloride, affording a nasal composition containing 15 mg of morphine sulfate per 0.1 ml.

Repetition of the procedure of the first paragraph of this example using 20 grams of pentazocine lactate in place of the nalbufine hydrochloride affords a nasal composition containing 20 mg of pentazocine lactate per 0.1 ml.

EXAMPLE 3

1 Gram of naltrexone is dissolved in 80 ml of isotonic saline solution and the pH of the resultant solution is adjusted to 7.0-7.2 with dilute hydrochloric acid. A quantity of isotonic saline sufficient to bring the total volume to 100 ml is then added, and the

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solution is sterilized by being passed through a 0.2 micron Millipore filter. The resultant composition contains 1 mg of naltrexone per 0.1 ml.

Repetition of the foregoing procedure utilizing 0.5 gram of levonantradol in place of the naltrexone affords a nasal composition containing 0.5 mg of levonantradol per 0.1 ml.

The procedure of the first paragraph of this example is substantially repeated, save that 4 grams of butorphanol are employed in place of the naltrexone, to afford a nasal composition containing 4 mg of butorphanol per 0.1 ml.

Substitution of 2 grams of cyclazocine for the naltrexone used in the first paragraph of this example and substantial repetition of the procedure there detailed afford a nasal composition containing 2 mg of cyclazocine per 0.1 ml.

EXAMPLE 4

80 Grams of water are heated to 80°C and 3.0 grams of Methocel are added, with stirring. The resultant mixture is allowed to stand at room temperature for 3 hours. Then, 1.5 grams of naloxone stearate are suspended in 20 grams of water, that suspension is added to the gel and thoroughly mixed, and the resultant viscous solution or gel is adjusted to isotonicity with sodium chloride. The sustained release composition thus obtained contains 1.5 mg of naloxone stearate per 0.1 ml.

The above procedure is substantially repeated, except that 2.0 rather than 3.0 grams of Methocel are employed, and 1.5 grams of naltrexone myristate are

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substituted for the naloxone stearate. The sustained release composition prepared in this manner contains 1.5 mg of naltrexone myristate per 0.1 ml.

Repetition of the procedure of the first paragraph of this example, but using 20 grams of nalbuphine palmitate in place of the naloxone stearate, affords a sustained release composition containing 20 mg of nalbuphine palmitate per 0.1 ml.

The procedure of the first paragraph of this example is substantially repeated, except that 3 grams of levorphanol stearate are employed in place of the naloxone stearate. The resultant sustained release composition contains 3 mg of levorphanol stearate per 0.1 ml.

Substitution of 4 grams of buprenorphine stearate for the naloxone stearate used in the first paragraph of this example and substantial repetition of the procedure there detailed afford a sustained release composition containing 4 mg of buprenorphine stearate per 0.1 ml.

In a similar manner, repetition of the procedure of the first paragraph of this example, but using 2.5 grams of butorphanol palmitate, 3.5 grams of pentazocine myristate, 10 grams of THC, 20 grams of CBD or 1 gram of levonantradol in place of the naloxone stearate affords a sustained release composition containing, respectively, 2.5 mg of butorphanol palmitate, 3.5 mg of pentazocine myristate, 10 mg of THC, 20 mg of CBD or 1 mg of levonantradol, per 0.1 ml.

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Similarly prepared are sustained release compositions containing long chain carboxylic acid salts (e.g. stearates) of levallorphan, nalorphine, cyclazocine, phenazocine and morphine and the other morphine analogues named herein.

EXAMPLE 5

The following are illustrative aqueous solutions of selected drugs suitable for use as nasal drops or nasal spray. In each case, the pH of the final composition is adjusted to 7.4. If desired, the solutions are adjusted to isotonicity

COMPOSITION A

Ingredient	Amount
nalbufine hydrochloride	1000 mg
Tween 80	4 mg
methylcellulose	40 mg
water, purified	10 ml

COMPOSITION B

Ingredient	Amount
nalorphine hydrobromide	500 mg
Tween 80	3 mg
methylcellulose	30 mg
water, purified	10 ml

COMPOSITION C

Ingredient	Amount
buprenorphine hydrochloride	100 mg
Tween 80	2 mg
methylcellulose	20 mg
water, purified	10 ml

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Naturally, the therapeutic dosage range for nasal administration of the drugs according to the present invention will vary with the size of the patient, the condition for which the drug is administered and the particular drug employed. Generally, the daily dosage will approximate the amounts previously employed for IV, IM or SC administration of the particular drug involved. Thus, a typical dose of buprenorphine would be 4-8 mg per day as a maintenance dose in the treatment of narcotic addicts. The quantity of nasal dosage form needed to deliver the desired dose will of course depend on the concentration of drug in the composition. The volume of solution or gel which would be needed to deliver the daily dose of buprenorphine specified above would be 0.1 to 0.2 ml of 4% solution or gel.

While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions and additions may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims.

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WHAT IS CLAIMED IS:

1. A pharmaceutically acceptable nasal dosage form for nasally delivering systemic therapeutic levels of drug to a warm-blooded animal which comprises (i) a systemically therapeutically effective amount of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, or Δ^9-tetrahydrocannabinol or a pharmacologically active analogue thereof bearing at least one phenolic hydroxyl substituent, and (ii) a nontoxic pharmaceutically acceptable nasal carrier therefor, said nasal dosage form comprising a nasal ointment or a nasal gel.

2. A dosage form according to Claim 1, said dosage form comprising a nasal gel.

3. A dosage form according to Claim 2, said dosage form comprising a sustained release nasal gel.

4. A dosage form according to Claim 1, 2 or 3, wherein (i) comprises a systemically therapeutically effective amount of naloxone, naltrexone, levallorphan, nalorphine, nalbufine, buprenorphine, butorphanol, cyclazocine, pentazocine, phenazocine, Δ^9-tetrahydrocannabinol, cannabidiol or levonantradol, or of a nontoxic pharmaceutically acceptable acid addition salt of naloxone, naltrexone, levallorphan, nalorphine, nalbufine, buprenorphine, butorphanol, cyclazocine, pentazocine or phenazocine.

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5. A dosage form according to Claim 1, 2 or 3, wherein (i) comprises a systemically therapeutically effective amount of Δ^9-tetrahydrocannabinol, cannabidiol or levonantradol.

6. A dosage form according to Claim 1, 2 or 3, wherein (i) comprises a systemically therapeutically effective amount of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity.

7. A dosage form according to Claim 6 wherein morphine or its analogue is in the form of a long chain carboxylic acid salt, the carboxylic acid portion of said salt containing from 10 to 20 carbon atoms.

8. A pharmaceutically acceptable sustained release nasal dosage form for nasally delivering systemic therapeutic levels of drug to a warm-blooded animal which comprises (i) a systemically therapeutically effective amount of a long chain carboxylic acid salt of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, and (ii) a nontoxic pharmaceutically acceptable nasal carrier therefor.

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9. A dosage form according to Claim 8, wherein (i) comprises a systemically therapeutically effective amount of a long chain carboxylic acid salt of naloxone, naltrexone, levallorphan, nalorphine, nalbufine, buprenorphine, butorphanol, cyclazocine, pentazocine or phenazocine.

10. A dosage form according to Claim 8 or 9, wherein the carboxylic acid portion of said salt contains 10 to 20 carbon atoms.

11. A dosage form according to Claim 10, wherein said salt is a stearate, palmitate or myristate.

12. A dosage form according to Claim 8 or 9, said dosage form comprising a nasal solution, nasal suspension, nasal ointment or nasal gel.

13. A pharmaceutically acceptable, isotonic nasal dosage form for nasally delivering systemic therapeutic levels of drug to a warm-blooded animal which comprises (i) a systemically therapeutically effective amount of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, or Δ^9-tetrahydrocannabinol or a pharmacologically active analogue thereof bearing at least one phenolic hydroxyl substituent, and (ii) a nontoxic pharmaceutically acceptable nasal carrier therefor, said nasal dosage form having been adjusted to isotonicity.

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14. A dosage form according to Claim 13, wherein (i) comprises a systemically therapeutically effective amount of naloxone, naltrexone, levallorphan, nalorphine, nalbufine, buprenorphine, butorphanol, cyclazocine, pentazocine, phenazocine, Δ^9-tetrahydrocannabinol, cannabidiol or levonantradol, or of a nontoxic pharmaceutically acceptable acid addition salt of naloxone, naltrexone, levallorphan, nalorphine, nalbufine, buprenorphine, butorphanol, cyclazocine, pentazocine or phenazocine.

15. A dosage form according to Claim 13 or 14, said dosage form comprising a nasal solution, nasal suspension, nasal ointment or nasal gel.

16. A dosage form according to Claim 13 or 14, said dosage form comprising a sustained release nasal dosage form.

17. A dosage form according to Claim 13 or 14, said dosage form comprising a sustained release nasal gel.

18. A dosage form according to Claim 13 or 14, said dosage form comprising nasal drops or a nasal spray.

19. A long chain carboxylic acid salt of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having

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narcotic analgesic, antagonist or agonist-antagonist activity, the carboxylic acid portion of said salt containing 10 to 20 carbon atoms.

20. A salt according to Claim 19 which is a salt of morphine, oxymorphone, buprenorphine, naloxone, nalorphine, nalbufine, naltrexone, hydromorphone, metopon, nalmexone, cyprenorphine, diprenorphine, desomorphine, dihydromorphine, levorphanol, butorphanol, cyclazocine, pentazocine, cyclorphan, phenazocine, levallorphan, oxilorphan, alazocine, phenomorphan, 3-hydroxy-N-methylmorphinan, metazocine, norlevorphanol, apomorphine, apocodeine, profadol, ketobemidone or hydroxypethidine.

21. A salt according to Claim 19 which is a salt of naloxone, naltrexone, levallorphan, nalorphine, nalbufine, buprenorphine, butorphanol, cyclazocine, pentazocine or phenazocine.

22. A salt according to Claim 19, 20 or 21 which is a stearate, palmitate or myristate.

23. A method for eliciting a therapeutic response in a warm-blooded animal which comprises nasally administering to said animal a therapeutically effective amount of morphine or an analogue thereof bearing at least one phenolic hydroxyl substituent and having narcotic analgesic, antagonist or agonist-antagonist activity, or Δ^9-tetrahydrocannabinol or a

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pharmacologically active analogue thereof bearing at least one phenolic hydroxyl substituent.

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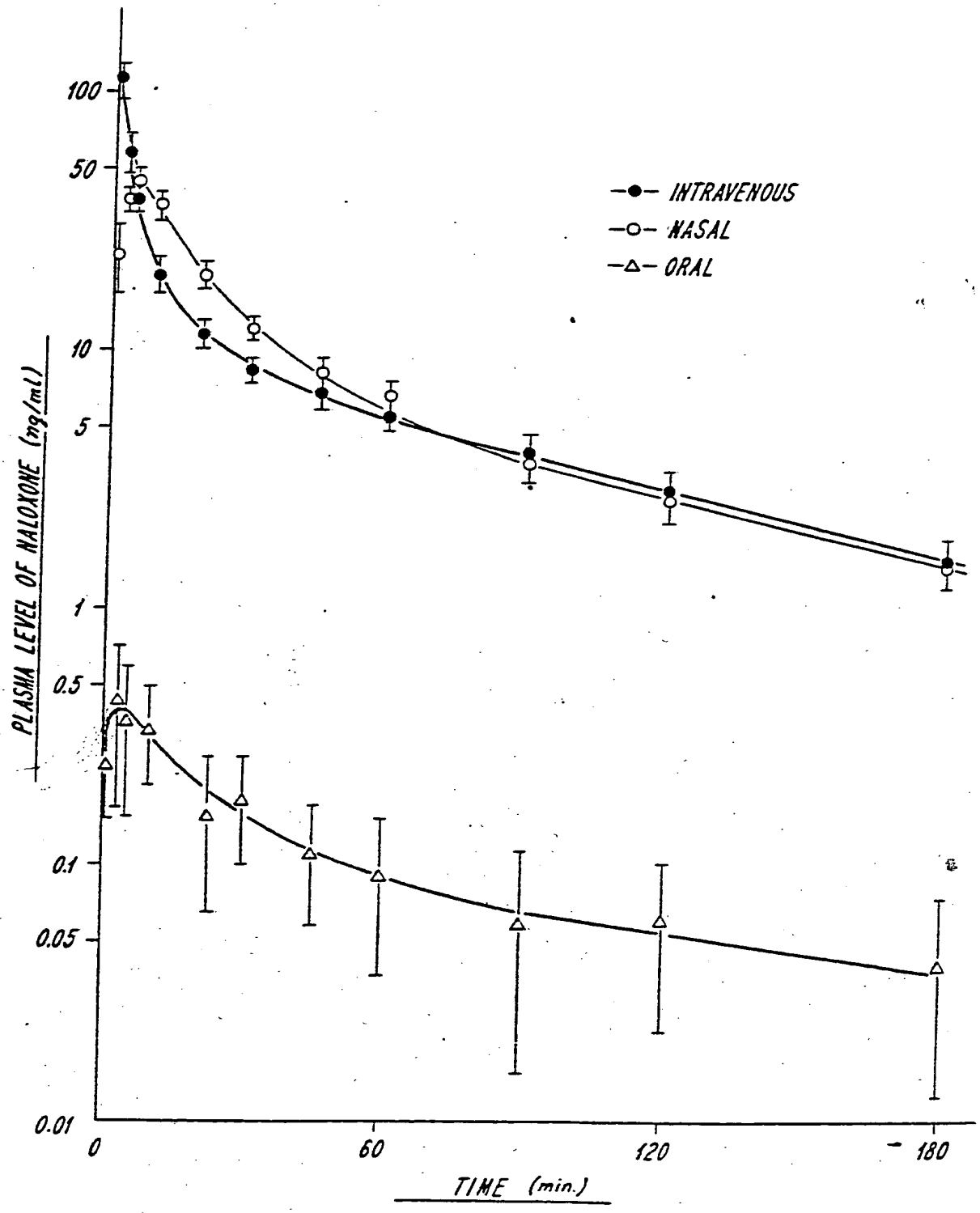
100
50
10
5
1
0.5
0.1
0.05
0.01
PLASMA LEVEL OF NALOXONE (ng/ml)
INTRAVENOUS
NASAL
ORAL
0
60
120
180
TIME (min.)

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/00546

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.[3] A61K 31/40, 31/47, 31/485
U.S. Cl. 424/258, 260, 274

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/258, 260 and 274

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
P, X	U.S. A, 4,275,059, Published 23 June 1981, Flora et al	1-23

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
16 AUG 1982	20 AUG 1982
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Stanley J. Friedman, Primary Examiner, Group Art Unit 125